# General

## Guideline Title

The role of biopsy in the management of patients with presumed diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline.

## Bibliographic Source(s)

Ragel BT, Ryken TC, Kalkanis SN, Ziu M, Cahill D, Olson JJ. The role of biopsy in the management of patients with presumed diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):481-501. [64 references] PubMed

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Regulatory Alert

## FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 14, 2016 – General anesthetic and sedation drugs : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.

# Recommendations

## Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Question

What is the optimal role of biopsy in the initial management of presumptive low-grade glioma in adults?

Target Population

Adult patients with imaging suggestive of a low-grade glioma.

Recommendation

*Level III*. Stereotactic biopsy is recommended when definitive surgical resection is limited by lesions that are deep-seated, not resectable, and/or located within eloquent cortex, or in patients unable to undergo craniotomy due to medical co-morbidities to obtain the critical tissue diagnosis needed for targeted treatment planning for patients with low-grade gliomas.

Question

What is the best technique for brain biopsy?

Target Population

Adult patients with imaging suggestive of a low-grade glioma.

Recommendation

*Level III*. Frameless and frame-based stereotactic brain biopsy (SBB) for low-grade gliomas are recommended based on clinical circumstances as they provide similar diagnostic yield, diagnostic accuracy, morbidity, and mortality. It is recommended the surgeon consider advanced imaging techniques (e.g., perfusion, spectroscopy, metabolic studies) to target specific regions of interest to potentially improve diagnostic accuracy.

Definitions

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence and Levels of Recommendation on Diagnosis

| | |
|---|---|
| **Class I evidence/Level I (or A) recommendation** | Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios |
| **Class II evidence/Level II (or B) recommendation** | Evidence provided by one or more well-designed clinical studies of a *restricted* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios |
| **Class III evidence/Level III (or C) recommendation** | Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios |

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Diffuse low grade glioma

## Guideline Category

Diagnosis

Evaluation

Management

## Clinical Specialty

Neurological Surgery

Neurology

Oncology

Pathology

Radiology

## Intended Users

Physicians

## Guideline Objective(s)

To evaluate relevant literature to formulate useful guidelines for the role of stereotactic brain biopsy (SBB) in the initial diagnosis of presumed low grade glioma (i.e., astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas)

## Target Population

Adult patients with imaging suggestive of a low-grade glioma

## Interventions and Practices Considered

1. Stereotactic brain biopsy (SBB) (frameless and frame-based)
2. Advanced imaging techniques (e.g., perfusion, spectroscopy, metabolic studies to target specific regions of interest)

## Major Outcomes Considered

- Morbidity
- Mortality
- Diagnostic accuracy
- Diagnostic yield

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

# Description of Methods Used to Collect/Select the Evidence

General Search Strategy

Literature Examination Approach

A wide-ranging literature search strategy was undertaken to identify all citations relevant to the management of low grade gliomas. The MEDLINE and EMBASE electronic databases were searched from 1990 through 2012, with additional data being gleaned from the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, and Cochrane Database of Abstracts of Reviews of Effects. The search strategies used a combination of subheadings and text words with the specifics of this work being outlined in each guideline section. Reference lists of the publications chosen for full text review were also screened for potentially relevant studies.

Study Selection

The search of the bibliographic databases identified possibly relevant citations for a given topic and often these were large in number. The eligibility (inclusion/exclusion) criteria to screen the citations for each of the questions were determined ahead of time for each section by the writing group. At least two authors evaluated the titles and abstracts using the inclusion and exclusion criteria with broad interpretation of the criteria being used initially so as to maximize the likelihood of capturing pertinent information. Cases of disagreement about pertinence were resolved by a third author when needed. The full text articles of the selected abstracts were then collected and the same process of applying the eligibility criteria was carried out again with the more in depth information available. Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Specific Search Strategy for This Guideline

Cochrane Central Register of Controlled Trials, the Cochrane Review, PubMed, and EMBASE literature searches from January 1, 1990, to December 31, 2012, encompassing "all fields" or "search all text" utilizing search strings to identify pertinent literature on biopsy of low grade glioma were undertaken. For PubMed the following search terms were used: low-grade glioma biopsy, LGG biopsy, stereotactic brain biopsy, brain biopsy sampling error, brain biopsy sampling errors, low-grade glioma sample error, and low-grade glioma sampling errors. For the Cochrane Central Register of Controlled Trials and EMBASE the following search terms were used: biopsy/and brain neoplasms/, brain neoplasms/and stereotactic techniques/, glioma/and stereotactic techniques/, and glioma/and biopsy. For the Cochrane Library the following search terms were used: low-grade glioma biopsy, stereotactic brain biopsy, biopsy and brain neoplasm, brain neoplasms and stereotactic techniques, glioma and stereotactic technique, and glioma and biopsy.

Eligibility Criteria

For literature to be included for consideration, the paper had to include adults (i.e., age 18 and above), with the following exclusion criteria:

- Non-English publications
- Basic science papers
- Animal studies
- Papers dedicated to pediatric gliomas (i.e., age less than 18)
- Papers describing only malignant or high-grade glioma (glioblastoma multiforme; GBM)
- Papers describing recurrent gliomas (recurrent astrocytoma, progressive astrocytoma)
- Papers focusing exclusively on surgery, chemotherapy, radiation or anesthesia, stereotactic guided surgical (e.g., stereotactic resection of arteriovenous malformation), psychiatric, infectious (e.g., acquired immunodeficiency syndrome [AIDS], human immunodeficiency virus [HIV], abscess, fungal), vascular, pathologic analysis (e.g., immunohistochemical staining), and spinal cord tumors

Because the published literature lacks large series of patients with presumed low grade glioma undergoing targeted stereotactic biopsies directed by advanced imaging modalities (e.g., perfusion, single-photon positron emission tomography [SPECT]), small cases series of fewer than 25 patients were included.

Study Selection

Following broad screening for relevance, two independent reviewers evaluated citations and full-text screening of potentially relevant papers using a priori criteria for data extraction on a standardized form. Disagreements were resolved with the involvement of a third reviewer, followed by

primary re-review until agreement was achieved.

## Number of Source Documents

An initial literature search resulted in 5800 articles. Exclusion criteria were applied to titles and abstracts resulting in 123 articles that underwent full-text review (see Fig. 1 in the original guideline document for a flowchart). A final 63 articles met all inclusion criteria and were used to formulate guidelines.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence and Levels of Recommendation on Diagnosis

| | |
|---|---|
| **Class I evidence/Level I (or A) recommendation** | Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios |
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| **Class III evidence/Level III (or C) recommendation** | Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios |

## Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

General Evidence Analysis

Quality Assessment and Statistical Methods

Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Studies which met the eligibility criteria were subject to more detailed scrutiny and had their data extracted by one reviewer and the extracted information was checked by one or more other reviewers. Evidence and summary tables, reporting the extracted study information and evidence classification, were generated for all of the included studies for each of the questions. Evidence tables were created with most recent data first and subsequent listings in retrograde chronological order. The table headings consisted of first author name and year, followed by a brief study description, chosen data class and conclusion. The authors were directed to craft the data in the tables in a succinct and fact filled manner so as to allow for understanding of the literature entry. The literature in the evidence tables was expanded upon in the scientific foundation of each section so as to emphasize important points supporting its classification and contribution to recommendations. The method by which this was accomplished is expanded upon in the Joint Guideline Committee Guideline Development Methodology document (see the "Availability of Companion Documents" field). Internal drafts of the tables and manuscripts were developed by sharing between writers electronically, by telephone and

meetings. Summary and conclusion statements were included for each section, with comments on key issues for future investigation being added where pertinent.

Specific Evidence Analysis for This Guideline

Study Selection and Quality Assessment

Following broad screening for relevance, two independent reviewers evaluated citations and full-text screening of potentially relevant papers using a priori criteria for data extraction on a standardized form. Disagreements were resolved with the involvement of a third reviewer, followed by primary re-review until agreement was achieved. Studies that met the eligibility criteria were extracted by one reviewer and this was then checked by a second reviewer.

Evidence Classification and Recommendation Levels

Both the quality of the evidence and the eventual strength of the recommendations generated by this evidence were graded according to a three-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee (see the "Rating Scheme for the Strength of the Evidence" field).

Articles were chosen that allowed for the calculation of two stereotactic brain biopsy (SBB)-specific parameters: diagnostic yield and diagnostic accuracy. In order to achieve Class I or II evidence, a well-designed SBB study had to calculate sensitivity and specificity values. Of note, given the inherent hemorrhage risk with brain biopsy, designing a double-blinded study with controls has yet to be done.

Diagnostic yield is the percent of stereotactic biopsies that obtain a histopathologic diagnosis. The "gold standard" for diagnostic yield was defined as the ability to obtain diagnostic tissue. Therefore, for diagnostic yield to achieve Class I or II evidence rating, a well-designed SBB trial would have to compare a targeting modality (i.e., surgical or imaging) with a SBB specimen.

Diagnostic accuracy is the proportion of stereotactic biopsies that agree with the "gold standard" of surgical resection or autopsy. For diagnostic accuracy, the Task Force defined the "gold standard" to be the comparison with brain tissue obtained at a subsequent craniotomy or at autopsy. Therefore, for diagnostic accuracy to achieve Class I or II evidence rating, a well-designed SBB trial would have to compare SBB with a surgical resection or autopsy brain specimen. Interestingly, surgical or autopsy specimens would never result in an incorrect histopathologic diagnosis, explaining why the calculated specificity and negative predictive values will always be 0%.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Guideline Panel Development

Recognizing the serious nature of low grade gliomas along with the lack of consensus among various treatment options, the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recommended that evidence-based guidelines be developed as a top priority, for the diagnosis, management and treatment of low grade glioma patients. The objectives of these guidelines are to establish the best evidence-based management of low grade gliomas in terms of imaging diagnosis, use of surgical biopsy and resection, assessment of tumor pathology, administration of systemic chemotherapy, and administration of radiation therapy. Because these tumors dependably recur or progress despite standard therapy, the Joint Tumor Section also recommended an evidence-based guideline be developed for progressive low grade gliomas and that information on promising emerging therapies be assessed in the same manner to determine the possible application of these findings.

Having identified the topical objectives, the Guidelines Committee of the Joint Tumor Section then recruited experts in the field from each of the parent organizations as lead writers of each section. These writers, in turn, recruited experts in non-neurosurgical specialties relevant to the field of management and therapy chosen. Writers were provided training on the method of guideline development as used in this guideline set by written methods and instructions. The senior authors and CNS Guidelines Manager then worked with them on a step by step basis to confirm that the methods were followed as the literature was collected, assessed and documents developed. When writers were approached and preliminarily agreed to participate they were asked to complete a formal conflict of interest questionnaire confirming the appropriateness of their participation. At that point they also agreed to report any new conflicts of interest that might develop during the writing process. In this manner a multidisciplinary panel of writers referred to as the Low Grade Glioma Guidelines Task Force was assembled, with significant administrative, logistical and

analytical support from the national CNS Guidelines Committee. The method of this evidence-based clinical practice parameter guideline has been written in a manner to be as transparent as possible using published assessment criteria.

Topic Range of This Systematic Review and Clinical Practice Guideline

Having identified writing groups for each topic, the members designed questions to allow assessment of the literature in a manner that would provide guidance for management of low grade gliomas. These questions are presented at the beginning of each of the eight guideline chapters spanning the topics of imaging assessment, diagnostic biopsy, surgical resection, tumor evaluation by standard neuropathology and molecular techniques, radiation therapy, chemotherapy, emerging therapies and treatment of recurrent or progressive low grade gliomas.

Guideline Panel Consensus

Multidisciplinary writing groups were created for each section based on author expertise, in order to address each of the disciplines and particular areas of therapy selected for these clinical guidelines. Each group was involved with literature selection, creation and editing of the evidence tables and scientific foundations for their specific section and discipline. Using this information, the writing groups then drafted the recommendations in answer to the questions formulated at the beginning of the process, culminating in the clinical practice guideline for their respective discipline. The draft guidelines were then circulated to the entire clinical guideline panel to allow for multidisciplinary feedback, discussion, and ultimately approval.

## Rating Scheme for the Strength of the Recommendations

See the "Rating Scheme for the Strength of the Evidence" field.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Approval Process

The completed evidence-based clinical practice guidelines for the management of low grade gliomas were presented to the Joint Guidelines Committee (JGC) of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) for review. The reviewers for the JGC were vetted by the *Journal of Neuro-oncology* for suitability and expertise to serve as reviewers for the purposes of publication in that journal also. The final product was then approved and endorsed by the executive committees of both the AANS and CNS prior to publication in the *Journal of Neuro-oncology*.

The funding agencies (CNS Executive Committee and AANS/CNS Joint Tumor Section Executive Committee) were permitted to review these guidelines only after the Joint Guidelines Committee had completed its extensive review, critique and ultimate approval process; the funding groups then were limited to whether or not to endorse or reject this body of work but substantive changes were not allowed.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Multiple studies underscore the importance of obtaining pathologic diagnosis prior to instituting treatment. Although surgical resection is the "gold standard" for histopathologic diagnosis, surgery may not be feasible in patients with tumors in difficult locations or patients too ill for craniotomy. In these cases, stereotactic brain biopsy (SBB) has been utilized.

## Potential Harms

- Morbidity and mortality related to biopsy. There is higher risk of biopsy-related morbidity in patients with diabetes mellitus, and thalamic and basal ganglia locations.
- Diagnostic inaccuracy is related to sampling error that can result in under- and over-estimation of tumor grade, as well as misdiagnosis.

# Contraindications

## Contraindications

Contraindications to stereotactic brain biopsy (SBB) in one reported study included: platelets <50,000/mL, international normalized ratio (INR) >1.5, coagulopathy, patients unable to cooperate with local anesthesia, patients unable to tolerate general anesthesia, lesions in which open or endoscopic surgery deemed less risky (e.g., pineal region).

# Qualifying Statements

## Qualifying Statements

The information in these guidelines reflects the current state of knowledge at the time of completion. Each section is designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

Ragel BT, Ryken TC, Kalkanis SN, Ziu M, Cahill D, Olson JJ. The role of biopsy in the management of patients with presumed diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):481-501. [64 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2015 Dec

## Guideline Developer(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

## Source(s) of Funding

These guidelines were funded exclusively by the Congress of Neurological Surgeons (CNS) Guidelines Committee, with no funding from any outside commercial sources. Development of this set of evidence-based clinical practice guidelines was editorially independent from the funding agencies.

## Guideline Committee

American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee

Low Grade Glioma Guidelines Task Force

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

Conflict of Interest

Low Grade Glioma Guidelines Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Disclosures

Dr. Kalkanis is a consultant for Arbor and Varian. Dr. Olson is a consultant for the American Cancer Society; has received research funding from the National Cancer Institute, Genentech, and Millennium; and has received investigational drug provision from Merck.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the Journal of Neuro-Oncology Web site .

## Availability of Companion Documents

The following are available:

- Rock J. Low grade glioma guidelines: foreword. J Neurooncol. 2015 Dec;125(3):447-8. Available from the Journal of Neuro-Oncology Web site .
- Olson JJ, Kalkanis SN, Ryken TC. Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: introduction and methods. J Neurooncol. 2015 Dec;125(3):449-56. Available from the Journal of Neuro-Oncology Web site .
- Congress of Neurological Surgeons (CNS). Guideline development methodology: endorsed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Guideline Committee. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2012 Feb. 12 p. [2 references]. Available from the Congress of Neurological Surgeons Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on July 7, 2016. The information was not verified by the guideline developer. This summary was updated by ECRI Institute on February 15, 2017 following the U.S. Food and Drug Administration advisory on general anesthetic and sedation drugs.

## Copyright Statement



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